Improved Internal Defibrillation Success With Shocks Timed to the Morphology Electrogram

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Background—A previous retrospective study by our group suggested that shocks timed to the upslope of the shocking lead electrogram improved defibrillation efficacy. The goal of this study was to prospectively determine whether defibrillation threshold could be reduced by use of an algorithm that timed shocks to the upslope of coarse ventricular fibrillation (test treatment) compared with shocks delivered asynchronously after 10 seconds of fibrillation (control treatment).

Methods and Results—Ten pigs were instrumented with a 3-lead system for internal defibrillation. Initial estimates of the energy required to achieve defibrillation E50 for both treatments were made by an up/down method. Subsequently, additional shocks at V50±10% and V50±20% were given for each treatment to obtain data points at higher and lower intensities. Probability-of-success curves were estimated for both treatments by the best-fit method. Energies required were significantly lower for the timed shocks than for the asynchronous shocks (P<0.001). E50 was reduced 15.5%, from 27.1±2.5 to 22.9±1.8 J (P<0.002). The width of the probability-of-success curve (E50−E20) for the test treatment was also significantly narrower than that for the control treatment (7.1±0.9 versus 10.8±1.7, P<0.01). Normalized curve width (E50−E20)/E50 was decreased from 51±5% of E50 for control shocks to 37±4% of E50 for synchronous shocks (P<0.02).

Conclusions—In this model, defibrillation threshold is lower and more deterministic when shocks are timed to the upslope of the shocking lead electrogram. If a similar reduction is observed in humans, shock timing may lower defibrillation threshold and simplify programming of shock intensity. (Circulation. 1998;98:808-812.)

Key Words: action potentials • defibrillation • electrophysiology • fibrillation

The amplitude of the fibrillation electrogram varies with time, showing periods of “coarse” (high-amplitude) and “fine” (low-amplitude) fibrillation. This variation has led to speculation that there might be opportune “windows” of time during which delivery of the defibrillating shock would have a higher probability of success. Kuelz et al1 suggested that defibrillation shocks delivered when the absolute voltage of the lead II ECG was high were more likely to succeed than those delivered when the absolute voltage was low. Their study used several sizes of “moving windows” to determine the absolute voltage. They determined that only a small window, which was shorter than the fibrillation cycle length, was predictive of success. Another new preliminary study confirmed that defibrillation success can be predicted with only small windows and even then, only in selected leads.2

We observed that with small averaging windows, which closely correlate with the actual electrogram morphology, shocks tend to be delivered on the upslope of the electrogram. This finding suggested that upslope morphology may be predictive of defibrillation success. Therefore, in a retrospective study,3,4 we examined the probability of success as a function of absolute fibrillation amplitude and upslope versus downslope morphology. We found no correlation between absolute amplitude of the fibrillation electrogram at the time of the shock and successful defibrillation. However, we did find that shocks were more likely to be successful if they were delivered on the upslope of the shocking lead electrogram rather than on the downslope (67% versus 39%).3 We also found that the morphology (upslope versus downslope) of the internal shocking lead electrogram, but not that of the external ECG leads, correlated with successful defibrillation.5 Therefore, the goal of this prospective study was to test the hypothesis that shocks delivered according to an algorithm that timed them to the upslope of the fibrillation electrogram recorded from the shocking electrodes have a lower defibrillation threshold than shocks delivered at a fixed time independent of electrogram morphology.

Animal Preparation
Swine (n=10; 32 to 38 kg) were preanesthetized with xylazine (2.0 mg/kg IM) and telazol (4.0 mg/kg IM), then anesthetized with...
sodium pentathol (10 to 20 mg/kg IV). Each animal was intubated and placed on a volume-controlled ventilator with a tidal volume of 10 to 14 mL/kg at 10 to 15 bpm. Isoflurane, delivered with O₂, was initially set at 2% and adjusted as needed to maintain anesthesia. Body temperature was maintained at 37°C with a water-heated pad. The animal was placed in a dorsal anatomic position. A peripheral intravenous line was introduced for administration of drugs and fluids. Limb leads were attached for ECG monitoring. An arterial line was established for monitoring blood pressure. Arterial blood pressure and blood gases (PCO₂, P O₂) were maintained within acceptable physiological ranges (arterial blood pressure=70 to 120, P CO₂=35 to 60, and P O₂=300 to 450 mm Hg).

An endocardial defibrillation lead, consisting of an RV and an SVC electrode, was inserted under fluoroscopic guidance through a left or right external jugular vein and positioned into the heart so that the tip was in the apex of the right ventricle. The leads were ligated to the vessels to prevent dislodgment. The swine was then rotated to a right lateral position and restrained with elastomeric cords to limit shock-induced movements during the defibrillation trials. A titanium can (55 mL), similar in size to an ICD, was positioned subcutaneously to the tip was in the apex of the right ventricle. The leads were ligated to the vessels to prevent dislodgment. The swine was then rotated to a right lateral position and restrained with elastomeric cords to limit shock-induced movements during the defibrillation trials. A titanium can (55 mL), similar in size to an ICD, was positioned subcutaneously to

The morphology signal was measured with the RV electrode as cathode and the SVC electrode and active pectoral can together as anode. This signal was amplified by a custom amplifier, digitized at 400 Hz, and analyzed by use of an algorithm developed in LabView (National Instruments Inc) for timing defibrillation shocks. All procedures were in accordance with institutional guidelines.

Defibrillation Shock Time Control: Algorithm Setup

The custom-designed LabView software generated a trigger signal that caused a defibrillation shock to be delivered whenever a selected condition on the amplified morphology signal was fulfilled. A schematic of the program used in this experiment is shown in Figure 1. The peak-to-peak amplitude of each fibrillation complex was defined as PPA. The algorithm ignored the first 4 seconds to allow time for fibrillation patterns to stabilize. It then monitored the PPA of each fibrillation complex between 4 and 9 seconds of fibrillation and determined the LPPA. After the monitoring period, the algorithm searched for a complex that exceeded an amplitude of 0.5 LPPA. Then the rule in Figure 1B was applied. This rule searched for a minimum amplitude, b, that was less than the point a that occurred 12.5 ms sooner. This defined the “trough.” When b was followed by the continuously increasing points c and d, indicating an upslope, and when d exceeded 0.5 LPPA, the shock was delivered. The sampling rate was 400 Hz, and the algorithm used every fifth sample for determining the PPA and upslope. Therefore, the samples used by the algorithm (shown by a, b, c, and d in Figure 1B) were 12.5 ms apart. This caused the shock to always be delivered at least 25 ms after point b.

Although our previous retrospective study showed that defibrillation efficacy was independent of high- or low-amplitude complexes at the time of the shock, the trigger for the synchronized shock was generated only when a high-amplitude complex preceded an upslope pattern. This rule was enforced because a second high-amplitude complex usually follows the first high-amplitude complex. Therefore, we could more easily time the shock, which occurred at least 25 ms after the trough, to be delivered on the upslope (rather than at a peak) by use of the algorithm. The user could select either the asynchronous control or the test treatment from the front panel of the program with the mouse. Control shocks were delivered according to the standard asynchronous clinical protocol 10 seconds after VF induction.

Defibrillation Protocol

A biphasic waveform (140 μF, 80% tilt) was used in this study. The shocking configuration was RV−(3.4 cm)→SVC+(6.8 cm)+Active-Can+. Fibrillation was induced with a 9-V battery. If a shock (test or control treatment) failed to defibrillate, a rescue shock of known efficacy was delivered. At least 3 minutes was allowed between fibrillation episodes. Control and test treatments were selected randomly with a random-number generator. Approximately 80 defibrillation shocks were delivered to each animal. The first 30 shocks were delivered with an up/down protocol. The initial shock amplitude was based on experience. Depending on the success or failure of this shock, amplitude was increased or decreased in steps of 20% until the first reversal. Then the up/down protocol was continued with a step size of 10% until 15 shocks were delivered. E 50 , V 50 , and I 50 were estimated from both a 5-reversal algorithm, which required as few as 6 shocks, and a best-fit algorithm, which used all 15 shocks. Then, to obtain additional shocks higher and lower on the probability curve so that curve width could be better estimated, additional shocks at fixed-intensity bins were delivered. The bins chosen were V 50±10% and V 50±20%, using the V 50 obtained with the best-fit algorithm.

Data Recording and Analysis

An NEC computer running the Codas program (DATAQ) was used to monitor the amplified morphology signal to allow real-time verification of the shock timing relative to the morphology lead electrogram. A TEAC RD130TE digital data recorder recorded the morphology signal and surface lead II ECG for retrospective analysis. For each shock, the outcome (success or failure), delivered energy, peak voltage and current, and cycle length just before the shock were determined. Probability-of-success curves were calculated by the best-fit method, which we have used previously. E 50 −E 20 was defined as the width of the probability-of-success curve. E 20 was defined as the normalized curve width.

Results

A total of 760 shocks were delivered to 10 animals. Half of these shocks were delivered with the test treatment and the other half with the control treatment. Figure 2 shows the
morphology and rate-sensing lead electrograms, as well as lead II from the surface ECG during a 13.7-J shock delivered with the timing algorithm, which led to a successful defibrillation. Figure 3 shows an expanded region around the shock and illustrates that the shock in this example was delivered on the upslope of the morphology lead electrogram. The algorithm delivered all shocks on the upper half of the upslope.

**Duration of VF**
The delivery time for control shocks was set at 10 seconds. All shocks were actually delivered at 10.7 ± 0.03 seconds. The timing algorithm attempted to deliver test shocks at 10 seconds. Actual shock delivery was at 12.7 ± 1.10 seconds.

**Probability-of-Success Defibrillation Curve**
The defibrillation threshold for both control and synchronized shocks was estimated by the up/down protocol described in the Methods section. Figure 4 compares the E50 determined by both a standard 5-reversal method (Figure 4A), which required as few as 6 shocks, and that determined by the best-fit method (Figure 4B), which required 15 shocks. The regression lines for both methods show that the defibrillation threshold for shocks delivered on the upslope is smaller than that for control shocks (the regression line is flatter than the unity line). However, the 95% CI for the best-fit method is much smaller than that for the 5-reversal method because of the greater number of shocks on which the estimate was based. Therefore, this method was used for estimating E50.

Dose-response curves for both the synchronized and random shocks were obtained by analyzing the shocks delivered at 10% and 20% higher and lower amplitudes than the original V50 estimate in combination with those obtained in the first part of the protocol. The curves were estimated by the best-fit method described in the Methods section. Figure 5 shows that curves for both synchronized and random shock timing followed the classic shape for defibrillation probability-of-success curves. However, the curve for the synchronized shocks was steeper and shifted toward lower threshold. Successful defibrillation required significantly less energy (P < 0.001 by repeated-measures ANOVA) when the shocks were delivered on the upslope of the morphology electrogram than when they were delivered with random timing. From E50 to E80, the defibrillation strength required for successful defibrillation with the synchronized shocks was statistically lower than that required for the control treatment (P < 0.05, Student-Newman-Keuls method).

**Individual Animals**
Figure 6 shows the paired E80 obtained from the probability curves for each individual animal. The mean shock intensity producing 80% success was reduced from 27.1 ± 2.5 to 22.9 ± 1.8 J (P < 0.002). All animals had a lower E80 when shocks were delivered coincidently with the upslope of the morphology electrogram than when they were delivered asynchronously. The improvement ranged from 4% to 25%; the 3 animals with the highest thresholds under control conditions had the greatest reduction in E80 when shocks were delivered on the upslope.

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**Figure 2.** Electrograms from morphology and rate-sensing leads and lead II of surface ECG recorded during a successful defibrillation.

**Figure 3.** Expanded view of same morphology electrogram as shown in Figure 2.

**Figure 4.** Defibrillation threshold for synchronized shocks (upslope) as a function of that for control shocks determined by 5-reversal method (A) and best-fit method (B). Lightly dotted line is a unity line predicting results if thresholds for upslope and control timing were equal. Solid line is first-order regression line obtained from data. Dashed lines are 95% CI.

**Figure 5.** Combined probability-of-success vs shock-intensity curves for 10 animals with synchronized (●) and random (○) timing.
Figure 7A shows the probability-of-successful-defibrillation curve width for each individual animal. The mean curve width was reduced from 10.8±1.7 to 7.1±0.9, P<0.01. The normalized curve width (Figure 7B) was reduced from 51±5% of E₈₀ for control shocks to 37±4% of E₈₀ for synchronized shocks (P<0.02). The 3 animals having the largest curve width for the asynchronous shocks had the greatest reduction in curve width when shocks were delivered on the upslope. These were the same animals that had the large reduction in E₈₀.

Discussion
Effects of Shock Timing on Defibrillation Threshold
Modern ICDs allow the operator to program the shock energy noninvasively. With these devices, it is desirable that the programmed energy be set as low as possible while still producing a high probability of successful defibrillation to reduce the size of the generator and prolong battery life. However, because the probability-of-success–versus–shock-intensity curve for defibrillation is usually broad and estimates of defibrillation threshold are only approximate, most operators set the ICD shock intensity at its maximum value.

Defibrillation efficacy can be improved by shifting the probability-of-success curve to the left or by making its slope sharper so that defibrillation threshold is more predictable. For example, the biphasic defibrillator waveforms, which have been adopted for internal defibrillators, are effective because they both move the probability curve to the left and make it steeper than corresponding monophasic waveforms.⁷

Another technique being explored to reduce defibrillation threshold involves timing of the shock to specific characteristics of the fibrillation waveform in various recording leads. An early study⁹ attempted to determine whether, during the periods of coarse fibrillation that alternate with periods of fine fibrillation, defibrillation threshold might be lower, because there are fewer wave fronts or myocardial activations are more synchronized. This study found no differences in synchronization of epicardial activations during periods of coarse or fine fibrillation and found both coarse and fine fibrillation at the same time in different leads. Another study by Carlisle et al¹⁰ showed no improvement in success of transthoracic defibrillation when shocks were synchronized to the peak or trough of the fibrillation waveform in lead II of the ECG.

Kuelz et al ¹ used an algorithm that timed the shock to the moving average of the AVFV in lead II of the ECG to predict defibrillation success. They found that higher values of AVFV were associated with improved defibrillation success and suggested that a higher value of AVFV corresponded to a higher degree of global depolarization. In their study, however, only very small time-averaging windows, which closely followed the actual electrogram morphology, were successful. It was our observation that with small averaging windows, the shock was likely to have been delivered on the upslope.

Our retrospective study ⁴ confirmed that a higher probability of success occurred when shocks were delivered on the upslope than when they were delivered on the downslope of the shocking lead electrogram (67% versus 39%). An improvement was observed only when shocks were timed to the shocking lead electrogram but not to the external ECG leads I, II, or III.⁵ The specificity to the shocking lead electrogram suggests that the local spatial distribution of depolarization at the time of the shock might be more important than a potential time-dependent state of global depolarization. The upslope characteristic of the shocking lead electrogram may correlate with a specific pattern of spatial fibrillation wavefront distribution and local action potential timing that increased the probability of a successful defibrillation.

The present study directly tested this hypothesis by comparing defibrillation probability-of-success curves when shocks were delivered asynchronously at random times as opposed to when they were delivered on the basis of an algorithm that timed the shock to the upslope of the shocking lead electrogram. The curve for shocks timed to the upslope was shifted to the left of that for the random shocks, so that E₈₀ occurred at a lower shock intensity. In addition, the probability-of-success curve was steeper, ie, had a smaller curve width, both unnormalized and normalized, when the
shock was delivered on the upslope, suggesting that timing to
the upslope may result in a more sharply defined defibrilla-
tion threshold. This more deterministic threshold may be
important in predicting the intensity at which a specific shock
will reach a high degree of success.

Importance of Using the Morphology Lead
During fibrillation, wave fronts circulate around the heart,
become blocked, and divide or change directions. Several
studies have suggested that, instead of hundreds of wave
fronts, perhaps only 2 or 3 wave fronts exist on the ventricle
at any given time and that the wave fronts may be larger than
previously thought.11,12 If the electrogram used for timing the
shock is recorded from the shocking electrodes, those regions
of the ventricle that contribute the most to the electrogram
signal would be those that are in the highest-current-density
regions during the shock. Cells in these regions would
therefore be most likely to be influenced by the shock to
produce defibrillation.

If only a few, large fibrillation wave fronts exist on the
ventricle, then the depolarization state of action potentials in
high-current-density regions may predict that of low-density
regions. Because the morphology channel that we recorded
from is configured so that the RV coil is cathodic and the
SVC and titanium can are anodic, a fibrillation wave front
that appears on the morphology channel as an upslope must
generally be moving from the RV coil to the SVC coil. This
suggests that the region near the RV coil must be repolariz-
ing. At this specific time, when cells in this high-current-
density region are repolarizing, cells in low-current-density
regions may be just beginning their action potential. If the
shock occurred at this time, then it would extend the refrac-
tory period of the cells in the high-current-density region that
are late in repolarization. In contrast, cells in the low-current-
density regions are early in their action potential at this
time. As a result, the refractory period is already long enough
to halt fibrillation wave fronts in these regions, even if the shock
is not strong enough to extend it.13 In agreement with this
hypothesis, we showed in a separate study that direct timing
of the defibrillating shock to monophasic action potentials
recorded from a low-voltage-gradient region also reduced
defibrillation threshold.4 When probability-of-success curves
were generated for “early” and “late” shocks, we found that
\( I_{sh} \) for early shocks was 17% lower than that for late shocks.
This corresponds to an \( \approx 30\% \) decrease in energy. In this
study, too, the largest decrease was found in those hearts with
the highest threshold.

In summary, the results of this study show that when ICD
shocks are timed to the upslope of the shocking lead electro-
gram, both defibrillation threshold (\( I_{sh} \)) and curve width of
the probability-of-success curve are reduced. If these findings
extend to clinical defibrillation, they may allow programming
of internal defibrillators at lower energies. This could reduce
potential postshock cardiac dysfunction, allow production of
smaller devices, and improve battery life.

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